REMARKS/ARGUMENTS

Rejections under 35 USC §112

In paragraph 3 of the office action, claims 1-4 and 16 are rejected under 35 USC 112 as failing to comply with the written description requirement. The examiner states (paragraph 5) that "the claimed method has been interpreted as encompassing the identification of 'diet-regulated disease-associated polynucleotides' as found in any life form, be it pant or animal, including humans." The examiner then states that "[t]he specification has not been found to provide an adequate written description of any "two different inbred genotypes" as they occur in humans, much less any and all life forms."

The applicant respectfully rebuts this rejection.

The applicant respectfully points out that the invention is not directed to the identification of 'diet-regulated disease-associated polynucleotides' as found in any life form, but only in mammals. This is clearly stated in claim 1.

Turning to the question of adequate description for the two different inbred genotypes required by claim 1, the examiner is respectfully directed to paragraphs 70-73 that describes providing two inbred strains of mice, exposing them to different diets, and more specifically to paragraphs 83-94 that particularly describes the use of two inbred strains of mice (obese yellow A^{vy}/A and agouti A/a), one strain of which is susceptible to obesity, hyperinsulinemia, and mammary cancer. The applicant asserts that the extensive description in the specification provides an adequate written description of two different inbred genotypes. The fact that this example used mouse strains, and does not refer to human or other mammal strains, does not undermine the adequacy of the written description provided. The fact that it would be difficult, unethical and practically impossible to perform the method of claim 1 using humans does not make the claim any less valid or well supported by the specification.

The concept of inbreeding has been known and understood by animal scientists for many decades. The term "inbred" is well understood in the art and is not indefinite. The International Committee on Standardized Nomenclature for Mice has ruled that a strain of mice can be considered "inbred" at generation F_{20} (See *Genetic Variants and Strains of the Laboratory Mouse, Committee on standardized genetic nomenclature for mice* (1989). Lyon, M. F. and Searle, A. G., eds. (Oxford University Press, Oxford), pp. 1-12). As stated in the MPEP ("TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT OF CHEMICAL/BIOTECHNICAL APPLICATIONS"):

"The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. E.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (Underlining added).

In the present case, the concept of inbred strains is well-known and best omitted.

Further, in paragraph 6 of the office action, the examiner states that the specification "fails to provide adequate written description of how such genes, even if expressed differently, are in fact associated with a disease."

The applicant respectfully points out that the very aim of the invention is to identify such diet-regulated, disease associated genes, and that this is done by the method described in the specification and in claim 1. The method is based on statistically significant quantitative differences in disease susceptibility between two different genotypes (in this case, inbred mouse strains). Specifically, two different inbred genotypes are selected (A and B). One of these

genotypes (A) is more susceptible to a disease (e.g., obese yellow A^{vy}/), and the other genotype (B) is less susceptible to the same disease (e.g., agouti A/a). Then each genotype is divided into two groups (A1 and A2 and B1 and B2). For one genotype, each group is fed a different diet (A1 is fed diet No.1 and A2 is fed diet No.2, and similarly for B1 and B2). Gene expression is then compared across the strains that differ in *either genotype or in diet, but not in both.* Thus A1 is compared with A2; A1 is compared with B1; but A1 is not compared with B2. Each experiment deals with only one variable at a time. Genes are identified that show significant changes in expression under these experimental conditions (e.g., a 2.0-fold or greater change in gene expression) and it is a premise of the experiment (and an inventor-defined term) that genes showing these characteristics are defined as being "diet-regulated, disease-associated genes." This is an eminently reasonable term since the genes that show such up- (or down-) regulation relative to the non-susceptible genotype, only show such characteristics in response to diet *in the disease-susceptible strain.*

The examiner states that the specification lacks adequate description of how factors such as race, age and sex are taken into account. The applicant respectfully draws examiner's attention to the above paragraph wherein the method is described clearly showing that the only variable being examined between the two species is diet and disease susceptibility. In all other respects, the individual subjects are the same.

Further, in paragraph 7 of the office action, the examiner states that "the applicant is attempting to satisfy the written description requirement ... through obviousness." The applicant respectfully and strongly rebuts this assertion and believes that the exemplary descriptions at paragraphs 70-73, paragraphs 83-94 and throughout the specification and in the claims are more than adequate to describe invention as required by 35 USC 112 and show that the applicant was in possession of the invention at the time of filing and to allow one of ordinary skill to practice the claimed invention. The applicant is in no way relying on obviousness. Claim 1 clearly describes the method of the invention. To state that the applicant is replying upon obviousness because certain terms in the claim are well known and understood is not reasonable or correct in law. The citation of University of California v. Eli Lilly & Co. (Fed. Cir 1997) is not supportive

of the examiner's position since the facts of that case (human insulin-encoding DNA was not described by a description of finding it) are quite different from the present case in which the claimed invention is the method for identifying certain genes, and not the genes themselves.

In paragraphs 8-10 of the office action, the examiner states that states that "the present case is analogous to that presented in Example 18 (pages 65-66) of the Written Description Guidelines (http://www.uspto.gov/web/menu/written.pdf)." The examiner states that "[u]nlike the example provided, the claims are not limited to a narrow genus that has been well described, but rather, fairly encompasses a vast, if not limitless genus of ... life forms ..." (at this point the writing becomes unclear).

Applicant respectfully asserts that this is incorrect. Contrary to the examiner's implications, Example 18 encompasses a large, if not limitless genus of polynucleotides (see claim 1: "...transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest...") any of which can be inserted into an expression vector and expressed in Neurospora crassa mitochondria. Likewise, in the present claimed invention, any mammalian polynucleotides can be screened for using the claimed method for identifying diet-regulated disease-associated polynucleotides. It is the method that is novel, and this method is well described and enabled by the claim and the supporting specification. The method can be employed with any mammalian polynucleotide. As in Example 18, the novelty is in the method steps, and it is the method that needs to be and is described and enabled. Not only does Example 18 does not support the examiner's assertions, but Example 18 is strongly supportive of the applicant's position, that the invention is adequately described.

For the sake of convenience and completeness of the record, example 18 is set out below (underlining added):

> "Example 18: Process claim where the novelty is in the method steps.
>
> Specification: The specification teaches a method for producing proteins using mitochondria from the fungus Neurospora crassa. In the method, mitochondria are isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a

protein of interest. The protein is subsequently expressed, the mitochondria is lysed, and the protein is isolated. The specification exemplifies the expression of alpha-galactosidase using the claimed method using a cytochrome oxidase promoter.

Claim:
1. A method of producing a protein of interest comprising;
obtaining Neurospora crassa mitochondria,
transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest,
expressing said protein in said mitochondria, and
recovering said protein of interest.

Analysis:
A review of the specification reveals that Neurospora crassa mitochondrial gene expression is essential to the function/operation of the claimed invention. A particular nucleic acid is not essential to the claimed invention.

A search of the prior art reveals that the claimed method of expression in Neurospora crassa is novel and unobvious.

The claim is drawn to a genus, i.e., any of a variety of methods that can be used for expressing protein in the mitochondria. There is actual reduction to practice of a single embodiment, i.e., the expression of A-galactosidase.

The art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.

The single embodiment is representative of the genus based on the disclosure of Neurospora crassa mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

Conclusion:
The claimed invention is adequately described."

In paragraphs 11-12 of the office action, claims 1-4 and 16 are rejected under 35 USC 112 as failing to comply with the enablement requirement. The examiner then sets out the Wands factors.

In paragraph 12, page 6 of the office action, under the heading "The quantity of experimentation necessary", the examiner suggests that the applicant was not in possession of the invention and states that the quantity of experimentation necessary to practice the invention would be "vast"

and would require "many man-years, if not decades, of trial an error research..." (paragraph 12 of the office action).

Applicant respectfully insists that this is simply not so. The quantity of experimentation required to perform the claimed method is minimal (if any is required at all). A reading of claim 1, step by step, together with the specification in which such an experiment is described, will make this clear.

> 1. A method for identifying diet-regulated disease-associated polynucleotides comprising the steps of:
>
> (i) selecting at least two different inbred known mammalian genotypes (A and B), one of these genotypes (A) being susceptible to a disease, and the other genotype (B) not susceptible to the same disease;

This step is potentially time-consuming, but poses no undue experimentation. The applicant has set out and described, in paragraphs 83-94 of the specification, the use of two inbred strains of mice (obese yellow Avy/A and agouti A/a), one strain of which is susceptible to obesity, hyperinsulinemia, and mammary cancer, the other of which is not. The inbreeding of mammals for the accentuation of certain traits has been done for centuries and is well known and routine. The modern ability to genetically manipulate mammals to cause susceptibility to diseases such as obesity, diabetes, Alzheimer's, Parkinson's, cancer, heart disease, etc., is well known and in fact such animal models are commercially available as inbred strains.

> (ii) dividing each genotype into two groups (A1 and A2 and B1 and B2);

Clearly this step does not require undue experimentation.

> (iii) for each genotype, each group is fed a different diet (A1 is fed diet No.1 and A2 is fed diet No.2, and similarly for B1 and B2);

Clearly this step does not require undue experimentation and is set out in great detail in the specification at paragraphs 79 et seq.

> (iv) measuring gene expression and comparing expression across the strains that differ in either genotype or in diet, but not in both;
>
> (v) analyzing the expression data so as to identify diet-regulated disease-associated genes.

These steps do not require undue experimentation. The method for measuring gene expressing at a genomic level using arrays is common and routine, and analyzing the date so as to identify diet-regulated disease-associated genes is thoroughly described in the specification at, for example, paragraph 85 et seq., in which the applicant describes using a factor of 2.5 as a significant threshold in the change in gene expression.

Under the heading "The amount of direction or guidance presented", the examiner acknowledges that "the specification provides an example whereby possible informative genes are identified in specific murine models." Then the examiner states that "No definitive results are provided which show that the genes are in fact "diet-regulated disease-associated polynucleotides."

This is simply not the case. The specification clearly and explicitly sets out experimentation and results that show that the genes identified are both regulated by diet and associated with a disease state. See paragraphs 76-89 and 90-103.

The applicant is at a loss to understand what more evidence the examiner could reasonably demand to show that the genes identified are in fact diet-regulated disease-associated polynucleotides. The very aim of the invention is to identify such diet-regulated, disease associated genes, and that this is done by the method described in the specification and in claim 1. The method is based on statistically significant quantitative differences in disease susceptibility between two different genotypes (in this case, inbred mouse strains). Specifically, two different inbred genotypes are selected (A and B). One of these genotypes (A) is more susceptible to a disease (e.g., obese yellow A^{vy}/), and the other genotype (B) is less susceptible to

the same disease (e.g., agouti A/a). Then each genotype is divided into two groups (A1 and A2 and B1 and B2). For one genotype, each group is fed a different diet (A1 is fed diet No.1 and A2 is fed diet No.2, and similarly for B1 and B2). Gene expression is then compared across the strains that differ in *either genotype or in diet, but not in both.* Thus A1 is compared with A2; A1 is compared with B1; but A1 is not compared with B2. (This answers the examiner's next question as to how various factors such as age, race, and sex are taken into account, as each experiment deals with only one variable at a time). Genes are identified that show significant changes in expression under these experimental conditions (e.g., a 2.0-fold or greater change in gene expression) and it is a premise of the experiment (and an inventor-defined term) that genes showing these characteristics are defined as being "diet-regulated, disease-associated genes." This is an eminently reasonable term since the genes that show such up- (or down-) regulation relative to the non-susceptible genotype, only show such characteristics in response to diet *in the disease-susceptible strain.*

The examiner further contends that even if diet-regulated disease-associated polynucleotides are identified, the specification "is silent as to how to use such a gene." See paragraph 12, page 6 of the office action.

With respect, it is the utility of the method, not of the genes identified, that is required to meet the threshold of 35 USC 101. If the examiner is suggesting that the method has no utility because identifying diet-regulated, disease-associated genes is of no commercial or therapeutic value, then the applicant vigorously rebuts such a contention. The identification of disease-related genes has been the subject very large amounts of work and money over many years by commercial laboratories. The utility of such identification includes, of course, the identification of potential therapeutic targets. Such utility, and therefore the utility of the invention, cannot reasonably be questioned.

With reference to claim 2, in paragraph 12, page 7 of the office action, the examiner states that "the specification does not provide the requisite independently derived set of diet-regulated and/or disease associated QTL's". The examiner goes on to quote Hybritech, underlining the

passage that says "However, when there is no disclosure of any specific starting material or any conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art."

Applicant respectfully points out that the rejection is in error. The specification does provide the requisite independently derived set of diet-regulated and/or disease associated QTL's. The present situation is not like that of Hybritech because there is adequate disclosure of specific starting material and there is disclosure of conditions under which the process can be carried out. Firstly, the QTLs are not themselves part of the invention. Claim 1 does not even require a step of QTL comparison. QTLs are only used to further support the identification of the gene already identified by the method of claim 1. The QTLs have been previously identified by others and QTLs for various phenotypes are well known and easily available. Secondly, the specification does indeed describe a large number of exemplary QTLs in Fig 3. The applicant certainly is not suggesting that the invention is to be practiced without guidance to particular materials such as QTLs as in the Hybritech case. The examples and the list of QTLs clearly enable the invention and undue experimentation would not be necessary to practice the claimed invention.

In paragraph 12, page 8 of the office action, under the heading "The nature of the invention", the examiner states that because the invention relates to matters of physiology and chemistry, that the invention requires "greater levels of enablement." The applicant realizes that biological systems are unpredictable in certain ways, but in the present case, the method as described and the type of results obtained from practicing the method are entirely reliable and "predictable". The expression of various genes with either be increased or decreased or stay the same within a certain set threshold. The methods are not susceptible to an unreasonable amount of unpredictability any more than any other biological or chemical analytical method. The specification provides sufficient enablement for the invention, and to raise the level of enablement to an arbitrary and unattainable threshold because the subject matter is biological or chemical is not within the scope of the rules or laws of patent examination procedure.

In paragraph 12, page 8 of the office action, under the heading "The state of the prior art", the examiner states that "...there is precious little work done in identifying genes that result in the identification of diet-regulated disease-associated polynucleotides.

Applicant respectfully points out that this statement is irrelevant. The whole purpose of the invention is to provide a method for the identification of diet-regulated disease-associated polynucleotides. There is no need for there to have been any pervious work in this field.

As for to the tools and methods used to practice the invention (expression analysis, arrays, inbreeding of mammals), such tools and methods are well understood and have been practiced for many years.

On page 8 of the office action, under the heading "The breadth of the claims", the examiner states that "the claims fairly encompass the identification of any manner of diet-regulated disease-associated polynucleotides in any life form, be it plant or animal, as well as plants that have been transformed so to express animal genes ...".

Applicant respectfully points out that this is incorrect. The claims are limited to mammals.

In paragraph 15-17 of the office action, claims 1-4 and 16 are rejected under 35 USC 112 as indefinite.

In paragraph 16 of the office action, the examiner states that "Claim 1 is indefinite with respect to what constitutes "inbred" genotypes as it relates to any life form be it plant of animal, including humans."

The term "inbred" is well understood in the art and is not indefinite. The International Committee on Standardized Nomenclature for Mice has ruled that a strain of mice can be considered "inbred" at generation F_{20} (See *Genetic Variants and Strains of the Laboratory Mouse, Committee on standardized genetic nomenclature for mice* (1989). Lyon, M. F. and Searle, A. G., eds. (Oxford University Press, Oxford), pp. 1-12).

In paragraph 17 of the office action, the examiner states that "Claim 1 is confusing as it relates to the benchmark to which "more" or "less" are being compared to." [sic.]. Applicant respectfully points out that...

Just because there terms are comparative, does not make them unclear. The concepts of "more" or "less" are so fundamentally and clearly understood as to need no further explanation.

To say that one genotype is more susceptible to a disease, and that another genotype is less susceptible to the same disease will generally have a clear meaning to one of skill in the art, as we tend to use strains of mice with great differences in disease susceptibility. For example, in the exemplary embodiment discussed in the specification employs the obese yellow A^{vy}/A mouse as the more disease-susceptible strain, and the agouti A/a as the less disease-susceptible strain.

Also it should be noted that the applicant has previously amended the claim to state that one genotype is more susceptible to a disease, and that another genotype is NOT susceptible to the same disease.

In paragraphs 18-19 of the office action, the examiner refers to the response of 11 July 2005 in which inbred mouse strains are used to exemplify an embodiment of the invention (as described in the specification). The examiner rejects this example stating that "the claims are not limited to mice, but rather, fairly encompass virtually any life form."

With respect, the applicant points out that this is not the case. The claims are limited to mammals. The mouse model is a well used and accepted model for genetic expression screening and the example provided provides methods that are suitable for use with any mammal with very little adaptation required.

Paragraph 20 of the office action does not appear to make sense. Clarification is requested.

Referring to paragraph 21, the examiner questions the utility of the invention under 35 USC 101.

The invention is a method for identifying diet-regulated disease-associated polynucleotides. Such a method, in itself, is clearly and undeniably useful. No further explanation should be required. The identification of disease-related genes has been the subject very large amounts of money over many years by commercial laboratories. The utility of such identification includes, of course, the identification of potential therapeutic targets.

Referring to paragraphs 22-23, the examiner states that "the specification is silent as to how one is to control for variables such as race and sex."

The applicant respectfully points out that the explicit methods of the invention require the use of siblings from inbred strains. The mice used were littermates (therefore their age was the same). Although the sex of the mice used is not specifically stated as being the same, this factor may be irrelevant to the experiment being performed. In such an experiment, variables are routinely minimized. Specifically, two different inbred genotypes are selected (A and B). One of these genotypes (A) is more susceptible to a disease (e.g., obese yellow A^{vy}/), and the other genotype (B) is less susceptible to the same disease (e.g., agouti A/a). Then each genotype is divided into two groups (A1 and A2 and B1 and B2). For one genotype, each group is fed a different diet (A1 is fed diet No.1 and A2 is fed diet No.2, and similarly for B1 and B2). Gene expression is then compared across the strains that differ in *either genotype or in diet, but not in both.* Thus A1 is compared with A2; A1 is compared with B1; but A1 is not compared with B2. Each experiment deals with only one variable at a time.

The examiner then states in paragraph 23 that "Even if the claims were to be limited to the use of a specific animal model, the specification is silent as to the genes of any one of these model [sic.] being an art-accepted model for any specific genes in any other life form.

Applicant is not completely clear as to the examiner's objection in this case, but respectfully draws the examiner's attention to the specification and tables attached thereto that set out a large

number of genes regulated by diet and involved in disease. The relationship between these genes and disease is "art-accepted". The fact the homologous and/or orthologous genes share similar functions is not in question.

Referring to paragraphs 24-25 the examiner states, with reference to QTL's that "[c]learly these are essential to practicing the claimed method, yet the specification is silent as to just what they are or how they are obtained." The examiner further states that "the applicant has not provided the requisite starting materials" to practice the claimed method."

First, the QTLs are not themselves part of the invention of claim 1. Claim 1 does not even require a step of QTL comparison. The applicant has previously pointed out this fact, in response to which the examiner states that "an independent claim must encompass that recited in the independent claim." It is not clear to the applicant what the examiner is trying to say. QTL's are not required to practice claim 1. QTLs are only used (in claim 2 et seq.) to further support the identification of the gene already identified by the method of claim 1. The QTLs have been previously identified by others and QTLs for various phenotypes are well known and easily available. Secondly, the specification does indeed describe a large number of exemplary QTLs in Fig 3. The examples and the list of QTLs enable the invention and undue experimentation would not be necessary to practice the claimed invention.

Referring to paragraphs 26-27 the examiner rejects applicant's definition of inbred as being achieved by in-breeding mice to the F_{20} generation. The examiner rejects the definition because the claims are not limited to mice and "no evidence has been presented as to how this would be applied in other life forms." The example employs mice, but the principal and methods of animal inbreeding are very well established. The application to mammals other than mice would require little or no adaptation of the methods.

Referring to paragraphs 28-30 the examiner rejects the reasoning and explanation of what "inbred" means as being merely attorney argument and therefore not evidence. The definition is quoted from an authoritative source. It is not attorney argument. (See *Genetic Variants and*

Strains of the Laboratory Mouse, Committee on standardized genetic nomenclature for mice (1989). Lyon, M. F. and Searle, A. G., eds. (Oxford University Press, Oxford), pp. 1-12). The authoritative source is used to demonstrate a well-established definition.

In view of the above reasoning, it is strongly believed that all the rejections should be withdrawn.

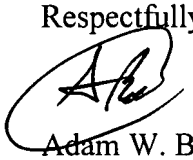
CONCLUSION

In view of the above reasoning, it is strongly believed that all the rejections should be withdrawn and that the claims are now in a condition for allowance.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-752-4085.

The Commissioner is hereby authorized to charge any calculated fee or any additional fees associated with this communication in particular and this application in general, and to credit any overpayment to Bell & Associates Deposit Account No. 50-3194

Respectfully submitted,



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